209. *Pyrazine Derivatives. Part XIII. Synthesis of 2-Aminopyrazine 1-Oxides by the Condensation of α-Amino-nitriles with Oximinomethyl Ketones.*

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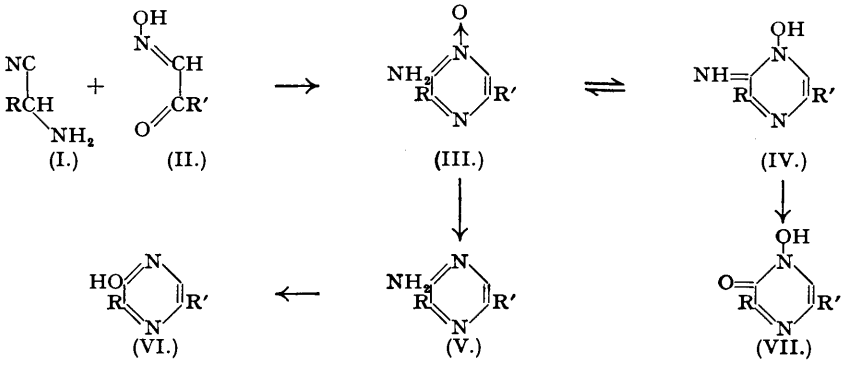
α-Amino-nitriles are shown to condense with oximinomethyl ketones to produce 3 : 5-disubstituted 2-aminopyrazine 1-oxides. This reaction affords a route to the synthesis of cyclic hydroxamic acids of the pyrazine series.

α-AMINOPROPIONITRILE (I; R = Me), liberated from its hydrochloride by the action of *N*-methylmorpholine, reacts in chloroform solution with oximinoacetone (II; R′ = Me) to form 2-amino-3 : 5-dimethylpyrazine 1-oxide (III; R = R′ = Me) [or 1 : 2-dihydro-1-hydroxy-2-imino-3 : 5-dimethylpyrazine (IV; R = R′ = Me)].



Treatment of 2-amino-3 : 5-dimethylpyrazine 1-oxide with aqueous ferric chloride gives a deep-blue colour which is discharged on addition of hydrochloric acid; in this respect it resembles 2-aminopyridine 1-oxide (Newbold and Spring, *J.*, 1949, S133). Reduction of 2-amino-3 : 5-dimethylpyrazine 1-oxide with sodium hydrosulphite (dithionite) gives 2-amino-3 : 5-dimethylpyrazine (V; R = R′ = Me) which reacts with nitrous acid to yield 2-hydroxy-3 : 5-dimethylpyrazine (VI; R = R′ = Me) identical with the product described by Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny (*J.*, 1949, 2707).

2-Amino-3 : 5-dimethylpyrazine 1-oxide forms an acetyl derivative, a picrate, a hydrochloride, and a salt with oximinoacetone. The last compound was encountered in the course of the reaction between α-aminopropionitrile and oximinoacetone; it is readily decomposed with dilute hydrochloric acid, and oximinoacetone can then be removed by ether extraction, and 2-amino-3 : 5-dimethylpyrazine 1-oxide recovered from the aquous solution.

2-Amino-5-ethyl-3-methylpyrazine 1-oxide (III or IV; R = Me, R′ = Et) was prepared in a similar manner from α-aminopropionitrile (I; R = Me) and ethyl oximinomethyl ketone (II; R = Et) (Sharp and Spring, *J.*, 1938, 1862). This compound has similar properties to its dimethyl homologue, its aqueous solution giving the blue colour reaction with ferric chloride. Similarly 2-amino-5-methyl-3-phenylpyrazine 1-oxide (III or IV; R = Ph, R′ = Me) was prepared in low yield from α-aminophenylacetonitrile (I; R = Ph) and oximinoacetone (II; R′ = Me), and likewise 2-amino-3-methyl-5-phenylpyrazine 1-oxide (III or IV; R = Me, R′ = Ph) was obtained in low yield from α-aminopropionitrile (I; R = Me) and oximinoacetophenone (II; R′ = Ph). The efficiency of the general reaction decreases with the replacement of alkyl by aryl groups, a point which is further emphasized by our inability to obtain 2-amino-3 : 5-diphenylpyrazine 1-oxide by the condensation of α-aminophenylacetonitrile and oximinoacetophenone.

Newbold and Spring (*loc. cit.*) have shown that 2-aminopyridine 1-oxide is not hydrolysed to the corresponding cyclic hydroxamic acid, 1-hydroxy-2-pyridone, on being heated with 10% aqueous potassium hydroxide. Under similar conditions we have found likewise that 2-amino-3 : 5-dimethylpyrazine 1-oxide (III or IV; R = R′ = Me) is not hydrolysed. With stronger alkali (40%), however, and prolonged heating, a small yield of the corresponding cyclic hydroxamic

acid, 1 : 2-dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine (VII; R = R′ = Me) was isolated and characterised as its copper salt.

Experimental.

2-Amino-3 : 5-dimethylpyrazine 1-Oxide.—A solution of *N*-methylmorpholine (4·38 c.c., 1 mol.) in dry chloroform (30 c.c.) was shaken with α-aminopropionitrile hydrochloride (4·26 g., 1 mol.), and oximinoacetone (3·48 g., 1 mol.) quickly added. The mixture was heated under reflux for 4 hours and filtered, and the chloroform evaporated under reduced pressure. A solution of the dark-brown liquid residue in water (25 c.c.) was treated with dilute hydrochloric acid (3N.; 25 c.c.), and the mixture filtered and extracted with ether (4 × 20 c.c.) to remove excess of oximinoacetone. The aqueous solution was made alkaline (litmus) with 2N-sodium hydroxide solution and evaporated to dryness, the alkalinity being maintained by the addition of further amounts of 2N-sodium hydroxide. The solid brown residue was dried, powdered, and extracted with boiling dry benzene (200 c.c.). When the benzene was removed and the residue dried over phosphoric oxide, *2-amino-3 : 5-dimethylpyrazine 1-oxide* (2·0 g.) was obtained as felted needles, m. p. 153—154°. For analysis it was sublimed at 110°/10^{-3} mm., forming a white felted mass, m. p. 156° (Found: C, 51·8; H, 6·7; N, 30·6. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%). 2-Amino-3 : 5-dimethylpyrazine 1-oxide hydrate separates as needles, m. p. 76°, on spontaneous evaporation of an aqueous solution or of solutions in wet solvents such as benzene. The hydrate slowly effloresces in air and rapidly loses water over phosphoric oxide to yield the anhydrous form, m. p. 156°. A concentrated solution of the hydrate in warm benzene sets to a gelatinous mass on cooling. 2-Amino-3 : 5-dimethylpyrazine 1-oxide is readily soluble in water, ethanol, methanol, and acetic acid, less soluble in ether or benzene, and only sparingly soluble in light petroleum (b. p. 60—80°). Its aqueous solution gives a deep-blue colour with a drop of aqueous ferric chloride, the colour being discharged by a drop of dilute hydrochloric acid. Light absorption in ethanol: Maxima at 3390 A. (ε = 7400) and 2340 A. (ε = 22,000). The *picrate* separates from ethanol as small, yellow prisms, m. p. 185° (Found: C, 39·4; H, 3·1; N, 22·75. $C_6H_9ON_3,C_6H_3O_7N_3$ requires C, 39·1; H, 3·3; N, 22·8%). The *hydrochloride* separates from ether or ethanol on the addition of ethereal hydrogen chloride, and when recrystallised from ethanol (charcoal) forms needles which char above 200° without melting (Found: C, 41·2; H, 5·8; N, 23·8. $C_6H_9ON_3,HCl$ requires C, 41·0; H, 5·7; N, 23·9%). The acetyl derivative was prepared by warming 2-amino-3 : 5-dimethylpyrazine 1-oxide with acetic anhydride for 30 minutes on the water-bath. The mixture was evaporated under reduced pressure, and after being kept the crystalline product was separated and recrystallised from dioxan (charcoal) from which the *acetyl* derivative separates as plates, m. p. 228° (Found: C, 53·5; H, 6·1; N, 23·15. $C_8H_{11}O_2N_3$ requires C, 53·1; H, 6·1; N, 23·2%). It is soluble in water, the solution giving a red colour with aqueous ferric chloride.

2-Amino-3 : 5-dimethylpyrazine 1-Oxide Oximinoacetone Salt.—(*a*) The salt was isolated from the mixture obtained in the preparation of 2-amino-3 : 5-dimethylpyrazine 1-oxide as described above. The dark-brown liquid obtained after removal of the chloroform was kept overnight and the large prisms of *N*-methylmorpholine hydrochloride separated. When the filtrate was stirred, smaller crystals separated which were collected and dried to constant weight over phosphoric oxide. This solid (1 part) was refluxed with dry light petroleum, (b. p. 60—80°; 200 parts), the *oximinoacetone* salt separating on the walls of the vessel as large needles, m. p. 96°. For analysis it was recrystallised from dry benzene and dried to constant weight over phosphoric oxide at room temperature; it then had m. p. 97° (Found: C, 48·2; H, 6·2; N, 24·6. $C_9H_{14}O_3N_4$ requires C, 47·8; H, 6·2; N, 24·8%). It was characterised by reaction in aqueous solution with dilute hydrochloric acid; oximinoacetone, m. p. 62° (undepressed when mixed with an authentic specimen) was extracted with ether, and 2-amino-3 : 5-dimethylpyrazine 1-oxide, m. p. 156° (undepressed when mixed with the product described above) was isolated from the acid aqueous solution by the previously described procedure. It is soluble in water, the solution giving the blue reaction with ferric chloride.

(*b*) 2-Amino-3 : 5-dimethylpyrazine 1-oxide (70 mg.) and oximinoacetone (43 mg.) were heated to 140° for 5 minutes. The melt was cooled and the solid refluxed with light petroleum (20 c.c.; b. p. 60—80°) whereupon the salt separated as clusters of needles on the vessel walls. After being dried (P_2O_5) at room temperature it had m. p. 96°, and a recrystallisation from benzene gave the salt as needles, m. p. 97° either alone or mixed with the specimen described under (*a*).

2-Amino-3 : 5-dimethylpyrazine.—A solution of 2-amino-3 : 5-dimethylpyrazine 1-oxide (300 mg.) in water (8 c.c.) was heated under reflux with sodium hydrosulphite (dithionite) (3·5 g.) (added in 0·5-g. portions, after cooling, each ½ hour) for 4 hours. The solution was made alkaline with sodium hydroxide solution and extracted with ether (6 × 10 c.c.). The ethereal solution was dried (Na_2SO_4) and evaporated, giving 2-amino-3 : 5-dimethylpyrazine hydrate as needles, m. p. 44° (130 mg.). The hydrate was kept over phosphoric oxide and sublimed twice at 60—80°/3 × 10^{-2} mm., to yield *2-amino-3 : 5-dimethylpyrazine* as small prisms, m. p. 96° (Found: C, 58·9; H, 7·5; N, 33·7. $C_6H_9N_3$ requires C, 58·5; H, 7·4; N, 34·1%). It is soluble in water and forms the hydrate (needles; m. p. 44—45°) when crystallised from wet light petroleum. It is readily soluble in alcohol, slightly soluble in benzene, and sparingly soluble in light petroleum (b. p. 60—80°), and it does not give a blue colour with the ferric chloride reagent. The *picrate* separates from ethanol in fine needles which char above 200° and melt with decomposition at 230—240° (Found: C, 40·8; H, 3·4. $C_{12}H_{12}O_7N_6$ requires C, 40·9; H, 3·4%).

2-Hydroxy-3 : 5-dimethylpyrazine.—A solution of 2-amino-3 : 5-dimethylpyrazine (62 mg.) in N-hydrochloric acid (2 c.c.), was treated at 0° with sodium nitrite (74 mg.) added gradually during 5 minutes. The solution was left at room temperature for 2 hours, then heated for 5 minutes at 60°, cooled, neutralised with sodium hydrogen carbonate, and evaporated to dryness. The solid residue, after being dried over calcium chloride, was extracted with boiling benzene (3 × 5 c.c.). On removal of the solvent the crystalline solid (10 mg.; prisms) was sublimed at 90°/10^{-3} mm. to yield 2-hydroxy-3 : 5-dimethyl-

pyrazine, m.p. 146° (Found : N, 22·8. Calc. for $C_6H_8ON_2$: N, 22·6%); the m.p. was undepressed when the sample was mixed with a specimen prepared by Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny (*loc. cit.*).

2-Amino-5-ethyl-3-methylpyrazine 1-Oxide was obtained from ethyl oximinomethyl ketone and α-aminopropionitrile hydrochloride using the procedure detailed above for the preparation of 2-amino-3 : 5-dimethylpyrazine 1-oxide, but omitting the drying procedure. *2-Amino-5-ethyl-3-methylpyrazine 1-oxide monohydrate* was obtained from benzene in glistening needles, m. p. 80—81° (Found : C, 49·4; H, 7·9; N, 24·7. $C_7H_{11}ON_3,H_2O$ requires C, 49·1; H, 7·7; N, 24·6%). After the hydrate had been kept over phosphoric oxide the *anhydrous base*, m. p. 109—110°, was obtained (Found : Loss in weight over P_2O_5, 10·3. $C_7H_{11}ON_3,H_2O$ requires H_2O, 10·5%). Its aqueous solution gives a blue colour with ferric chloride; this is discharged by dilute hydrochloric acid. Light absorption in ethanol : Maxima at 3370 A. (ε = 8100) and 2340 A. (ε = 28,500).

2-Amino-5-methyl-3-phenylpyrazine 1-Oxide.—From α-aminophenylacetonitrile hydrochloride and oximinoacetone, by use of the procedure detailed above for the preparation of 2-amino-3 : 5-dimethylpyrazine 1-oxide, a brown solid product was obtained on evaporation of the final benzene extract. This was washed with ethanol and recrystallised from the same solvent (charcoal), giving *2-amino-5-methyl-3-phenylpyrazine 1-oxide* as prismatic needles, m. p. 163—164° (Found : C, 65·3; H, 5·4; N, 20·95. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9%). It was nearly insoluble in water, but readily soluble in ethanol, the solution giving a blue colour, discharged by dilute hydrochloric acid, with a drop of aqueous ferric chloride.

*2-Amino-3-methyl-5-phenylpyrazine 1-Oxide.**—Condensation of α-aminopropionitrile hydrochloride and oximinoacetophenone was effected by using the general procedure described above with the modification that the reflux time was increased to 8 hours. The chloroform solution was evaporated to dryness and the residue extracted with dilute hydrochloric acid. Examination of this extract by the ferric test failed to disclose the presence of the 2-aminopyrazine 1-oxide. The acid-insoluble solid proved to be mainly oximinoacetophenone but gave a bluish-green coloration in the ferric test indicative of the presence of the required 2-aminopyrazine 1-oxide. A solution of the solid in a slight excess of 2N-sodium hydroxide solution was evaporated, and the solid residue dried and extracted with dry boiling benzene. The gummy brown solid obtained on removing the benzene gave an intense blue colour in aqueous-ethanolic ferric chloride. Two extractions of the brown solid with light petroleum (b. p. 60—80°) removed much of the sticky impurity. The solid was crystallised from acetone (charcoal) and heated at $100°/2 \times 10^{-3}$ mm. for 1 hour. The residue was crystallised from ethanol, giving *2-amino-3-methyl-5-phenylpyrazine 1-oxide* as prisms, m. p. 188—189°. For analysis it was sublimed at $150°/10^{-4}$ mm.; it then had m. p. 189° (Found : N, 21·1. $C_{11}H_{11}ON_3$ requires N, 20·9%). A solution of 2-amino-3-methyl-5-phenylpyrazine 1-oxide in ethanol gives a deep blue colour with ferric chloride, discharged by dilute hydrochloric acid.

1 : 2-Dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine.—2-Amino-3 : 5-dimethylpyrazine 1-oxide (1 g.) in water (4 c.c.) was treated with a solution of sodium hydroxide (4 g.) in warm water (1·5 c.c.). A yellow solid separated and the mixture was heated under reflux in an oil-bath at 140° for 22 hours, during which time ammonia was evolved. The cold mixture was diluted with water, nearly neutralized with hydrochloric acid, and evaporated to dryness. The alkaline solid residue was dried, powdered, and extracted with dry chloroform (3 × 30 c.c.) to remove unchanged 2-amino-3 : 5-dimethylpyrazine 1-oxide. The residue was dissolved in water, and the solution adjusted to pH 4 with hydrochloric acid and evaporated to dryness, additions of hydrochloric acid being made at intervals to maintain the pH at 4·0. The solid residue was dried, powdered, and extracted with dry chloroform (3 × 30 c.c.). Removal of the solvent gave an orange-brown solid (300 mg.) which on sublimation at $140°/5 \times 10^{-3}$ mm. gave 1 : 2-dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine, m. p. 124—126°, not depressed when mixed with a specimen, m. p. 135°, prepared by Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny (*loc. cit.*). The compound gave an acid reaction with litmus, effervesced with sodium hydrogen carbonate solution, and gave an intense wine-red colour in aqueous or alcoholic solution with ferric chloride solution. It was characterised by conversion into its copper salt. A solution (pH 4·0) of the crude hydroxamic acid (300 mg.) in hydrochloric acid was treated with saturated aqueous cupric acetate solution, and the green precipitate was filtered off, washed, dried (250 mg.), and crystallised twice from hot dioxan (1 : 200) to yield the *copper salt* of 1 : 2-dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine as tufts of prismatic needles, which charred without melting at *ca.* 275° (Found : C, 42·0; H, 4·1; N, 16·8. $C_{12}H_{14}O_4N_4Cu$ requires C, 42·2; H, 4·1; N, 16·4%). A solution of the salt in dioxan gives an orange-red colour with aqueous ferric chloride solution.

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* This experiment was made by Miss Sheila M. Gray, B.Sc.